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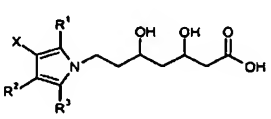
(54) Title: PROCESS AND INTERMEDIATE COMPOUNDS USEFUL IN THE PREPARATION OF STATINS, PARTICULARLY ATORVASTATIN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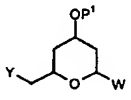
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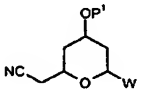
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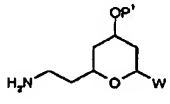
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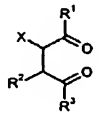
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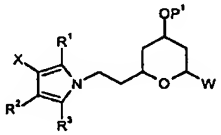
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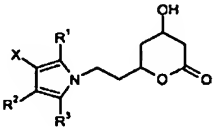
(6)

(57) Abstract: There is provided a process for the preparation of a compound of formula (7) or salts thereof: wherein R^1 represents a hydrogen or a hydrocarbyl group, R^2 represents a hydrogen or substituent group, R^3 represents a hydrogen or a hydrocarbyl group, and X represents a hydrogen or substituent group which comprises a) cyanating a compound of formula (1): wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or -OP^2, in which P^2 represents hydrogen or a protecting group, to give a compound of formula (2): b) reducing the compound of formula (2) to give a compound of formula (3): coupling the compound of formula (3) with a compound of formula (4): to give a compound of formula (5): when W represents -OP^2, deprotecting and then oxidising the compound of formula (5) to give a compound of formula (6): and e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, and removal of any remaining protecting groups, to give a compound of formula (7) or salts thereof.

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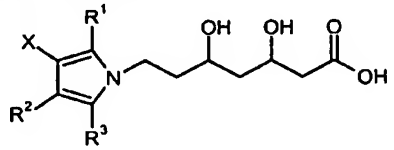
PROCESS AND INTERMEDIATE COMPOUNDS USEFUL IN THE PREPARATION OF STATINS, PARTICULARLY ATORVASTATIN

The present invention concerns a process and intermediate compounds useful in the preparation of statins, particularly atorvastatin.

According to the present invention, there is provided a process for the preparation of a compound of formula (7) or salts thereof:

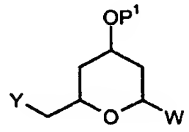


wherein

R^1 represents a hydrogen or a hydrocarbyl group
R^2 represents a hydrogen or substituent group
R^3 represents a hydrogen or a hydrocarbyl group
X represents a hydrogen or substituent group

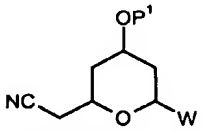
which comprises

a) cyanating a compound of formula (1):

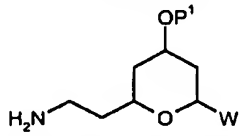


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group,

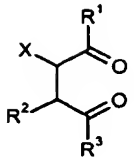
to give a compound of formula (2):



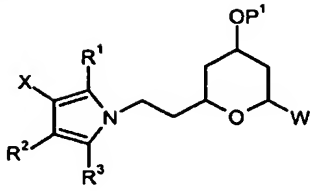
b) reducing the compound of formula (2) to give a compound of formula (3):



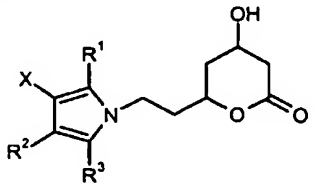
c) coupling the compound of formula (3) with a compound of formula (4):



to give a compound of formula (5):

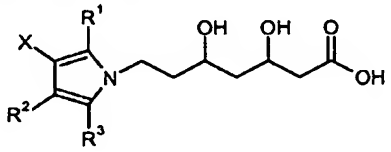


d) when W represents $-OP^2$, deprotecting and then oxidising the compound of formula (5) to give a compound of formula (6):



and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, and removal of any remaining protecting groups, to give a compound of formula (7) or salts thereof:



Hydrocarbyl groups which may be represented by R^1 and R^3 independently include alkyl, alkenyl and aryl groups, and any combination thereof, such as aralkyl and alkaryl, for example benzyl groups.

Alkyl groups which may be represented by R^1 and R^3 include linear and branched alkyl groups comprising up to 20 carbon atoms, particularly from 1 to 7 carbon atoms and preferably from 1 to 5 carbon atoms. When the alkyl groups are branched, the groups often comprising up to 10 branch chain carbon atoms, preferably up to 4 branch chain atoms. In certain embodiments, the alkyl group may be cyclic, commonly comprising from 3 to 10 carbon atoms in the largest ring and optionally featuring one or more bridging rings. Examples of alkyl groups which may be represented by R^1 and R^3 include methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, t-butyl and cyclohexyl groups.

Alkenyl groups which may be represented by R^1 and R^3 include $C_{2\text{-}20}$, and preferably $C_{2\text{-}6}$ alkenyl groups. One or more carbon - carbon double bonds may be

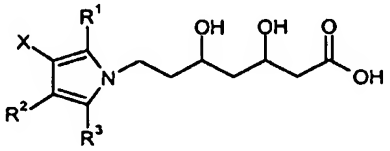
present. The alkenyl group may carry one or more substituents, particularly phenyl substituents. Examples of alkenyl groups include vinyl, styryl and indenyl groups.

Aryl groups which may be represented by R^1 and R^3 may contain 1 ring or 2 or more fused rings which may include cycloalkyl, aryl or heterocyclic rings. Examples of aryl groups which may be represented by R^1 and R^3 include phenyl, tolyl, fluorophenyl, chlorophenyl, bromophenyl, trifluoromethylphenyl, anisyl, naphthyl and ferrocenyl groups.

When any of R^1 and R^3 is a substituted hydrocarbyl group, the substituent(s) should be such so as not to adversely affect the rate or selectivity of any of the reaction steps or the overall process. Optional substituents include halogen, cyano, nitro, hydroxy, amino, thiol, acyl, hydrocarbyl, heterocyclyl, hydrocarbyloxy, mono or di-hydrocarbylamino, hydrocarbylthio, esters, carbamates, carbonates, amides, sulphonyl and sulphonamido groups wherein the hydrocarbyl groups are as defined for R^1 above. One or more substituents may be present. Examples of R^1 or R^3 groups having more than one substituent present include $-CF_3$ and $-C_2F_5$.

Substituent groups which may be represented by X and R^2 independently include hydrocarbyl groups as defined above for R^1, electron donating groups, electron withdrawing groups, halogens and heterocyclic groups. Substituent groups are commonly selected from the group consisting of optionally substituted alkoxy (preferably C_{1-4}-alkoxy), optionally substituted aryl (preferably phenyl), optionally substituted aryloxy (preferably phenoxy), polyalkylene oxide (preferably polyethylene oxide or polypropylene oxide), carboxy, phosphato, sulpho, nitro, cyano, halo, ureido, $-SO_2F$, hydroxy, ester, $-NR^aR^b$, $-COR^a$, $-CONR^aR^b$, $-NHCOR^a$, $-OCONR^aR^b$, carboxyester, sulphone, and $-SO_2NR^aR^b$ wherein R^a and R^b are each independently H, optionally substituted aryl, especially phenyl, or optionally substituted alkyl (especially C_{1-4}-alkyl) or, in the case of $-NR^aR^b$, $-CONR^aR^b$, $-OCONR^aR^b$ and $-SO_2NR^aR^b$, R^a and R^b may also together with the nitrogen atom to which they are attached represent an aliphatic or aromatic ring system; or a combination thereof.

Preferably, there is provided a process for the preparation of a compound of formula (7) or salts thereof:



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group

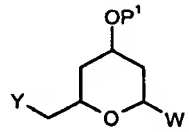
R^2 represents an aryl group, preferably a phenyl group

R^3 represents an aryl group, preferably a 4-fluorophenyl group

X represents a group of formula –COZ, wherein Z represents -OR^4, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or –NR^5R^6, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl

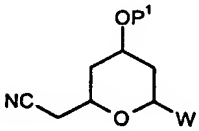
which comprises

a) cyanating a compound of formula (1):

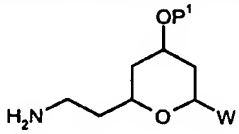


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or –OP^2, in which P^2 represents hydrogen or a protecting group,

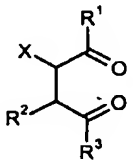
to give a compound of formula (2):



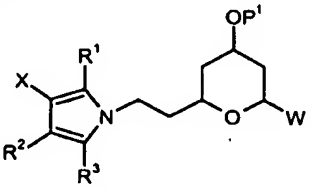
b) reducing the compound of formula (2) to give a compound of formula (3):



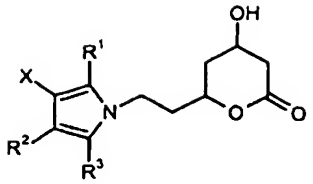
c) coupling the compound of formula (3) with a compound of formula (4):



to give a compound of formula (5):

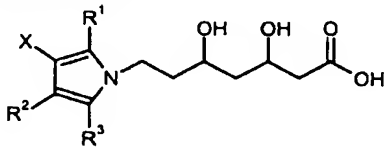


d) when W represents -OP^2, deprotecting and then oxidising the compound of formula (5) to give a compound of formula (6):



and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, and removal of any remaining protecting groups, to give a compound of formula (7) or salts thereof:



More preferably R^1 is an isopropyl group, R^2 is a phenyl group, R^3 is a 4-fluorophenyl group and X is a $-CO_2Me$, $-CO_2Et$ or -CONHPh group.

Protecting groups which may be represented by P^1 and P^2 include alcohol protecting groups, examples of which are well known in the art. Particular examples include tetrahydropyranyl groups. Preferred protecting groups are silyl groups, for example triaryl- and especially trialkylsilyl groups, and hydrocarbyl groups. Especially preferred are benzyl, methyl, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl groups.

Protecting groups which may be represented by P^1 and P^2 may be the same or different. When the protecting groups P^1 and P^2 are different, advantageously this may allow for the selective removal of only P^1 or P^2. Preferably, when the protecting groups P^1 and P^2 are different, P^1 is a benzyl or silyl group and P^2 is a methyl group.

Cyanation of compounds of formula (1) can be achieved by methods known in the art for displacing a halo group with a cyanide. Preferably, the process comprises contacting the compound of formula (1) with a source of cyanide. Preferred sources of cyanide include cyanide salts, especially ammonium or alkali metal cyanides, particularly sodium or potassium cyanide. A particularly preferred process comprises contacting the compound of formula (1) with 5 molar equivalents of KCN in the presence of dimethylsulfoxide solvent at a temperature of, for example, from 50 to 120°C preferably from 60 to100°C and more preferably from 70 to 90°C, typically about 80°C.

Reduction of compounds of formula (2) can be achieved using reduction systems known in the art for the reduction of nitrile groups. Preferred reductions systems include reduction with Raney nickel and hydrogen, reduction with hydrogen in the presence of a catalyst, such as palladium on carbon, reduction using hydride reagents, such as LiAlH4. Most preferred is reduction using boranes such as borane-THF. When palladium on carbon catalysed hydrogenation is employed, preferred conditions comprise the use of

methanol solvent at elevated temperature, such as about 40°C, in the presence of from about 0.01 to 100 molar equivalents of ammonia.

The coupling of the compound of formula (3) with the compound of formula (4) may employ conditions analogous to those given in WO89/07598 for the corresponding coupling. The conditions preferably comprise refluxing the compounds of formula (3) and (4) in a hydrocarbon solvent, such as toluene or cyclohexane, or mixtures thereof, followed by contact with aqueous acid, such as aqueous HCl.

When W represents OP^2, the protecting group may be removed to form a hydroxy group by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride, and benzyl groups may be removed by hydrogenolysis, such as reaction with hydrogen in the presence of palladium on carbon.

Oxidation of compounds formed by deprotection of compounds wherein W represents $-OP^2$ may employ conditions known in the art for the oxidation of pyranols to pyranones, and include those given in "Comprehensive Organic Transformations", R.C. Larock, 2nd Ed (1999) p 1670, published by Wiley VCH, incorporated herein by reference. Preferred oxidation systems include Ag_2CO_3/Celite, especially Celite J2 (with Ag2CO3), bromine, Swern oxidation or Dess-Martin periodinane oxidation.

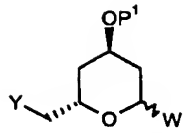
Ring opening of the compounds of formula (5), when W represent =O or formula (6) may employ conditions known in the art for ring opening of a pyranone. Preferably, the ring is opened by contact with a base, such as sodium hydroxide. Methanol is conveniently employed as solvent.

Remaining protecting groups may be removed by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride, benzyl ethers may be removed by hydrogenolysis, and methyl acetals may be removed by treatment with dilute aqueous acid.

It will be recognised that when X represents a group of formula $-COOR^4$, this may be converted to a group wherein X represents $-CONR^5R^6$ at any stage during the process, for example by reaction of the corresponding compounds of formulae (4), (5), (6) or (7) with a compound of formula HNR^5R^6.

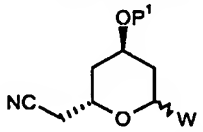
It will also be recognised that compounds of formulae (2) and (3) may also be subjected to oxidation (when W represents –OH) or deprotection and oxidation (when W represents (-O-protecting group) to form the corresponding compound wherein W represents =O.

Preferred compounds of formula (1) are compounds of formula:



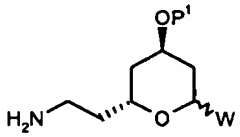
wherein W, P^1 and Y are as previously described.

Preferred compounds of formula (2) are compounds of formula:



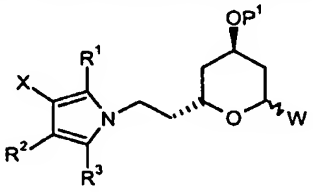
wherein W and P^1 are as previously described.

Preferred compounds of formula (3) are compounds of formula:



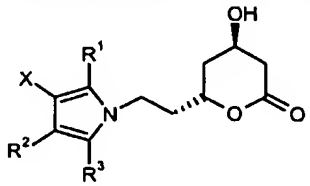
wherein W and P^1 are as previously described.

Preferred compounds of formula (5) are of formula:



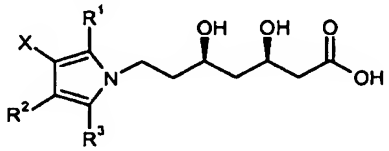
wherein R^1, R^2, R^3, W, X and P^1 are as previously described.

Preferred compounds of formula (6) are of formula:



wherein R^1, R^2, R^3, and X are as previously described.

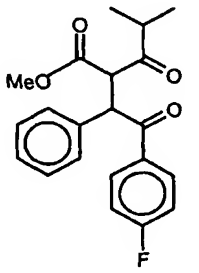
Preferred compounds of formula (7) are of formula:



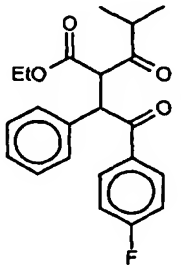
wherein R^1, R^2, R^3, and X are as previously described.

Compounds of formula (7) are advantageously converted to pharmaceutically acceptable salts, especially their calcium salts.

Compounds of formula (4) are advantageously prepared by the methods given in J. Med. Chem., 1991, **34**, pp357-366. Particularly preferred compounds of formula (4) are compounds of formula:



or



Compounds of formula (1) are advantageously prepared by enzyme catalysed condensation of acetaldehyde and 2-haloacetaldehyde, for example using the method given in US patent 5,795,749.

Compounds of formulae (2) and (3) and, when W is OP^2, formula (5) form further aspects of the present invention.

In preferred Compounds of formula (2) and (3) P^1 is a protecting group and preferably W represents $-OP^2$. When P^1 is a protecting group and W represents $-OP^2$, preferably P^1 and P^2 are different.

More preferred compounds of formula (2) and (3) are compounds where P^1 is a benzyl or silyl group and W represents OP^2 where P^2 is a methyl group.

Preferred compounds of formula (5) are compounds where P^1 is hydrogen, benzyl or silyl group and W represents =O or OP^2 where P^2 is a methyl group.

More preferred compounds of formula (5) are compounds where R^1 is a C_{1-6}alkyl group, R^2 is an aryl group, R^3 is an aryl group, X is COZ where Z is OR^4 where R^4 is an alkyl group or Z is NR^5R^6 where and R^5 and R^6 each independently is hydrogen alkyl or aryl, P^1 is hydrogen, benzyl or silyl group and W represents =O or OP^2 where P^2 is a methyl group.

Most preferred compounds of formula (5) are compounds where R^1 is an isopropyl group, R^2 is a phenyl group, R^3 is 4-fluorophenyl aryl group, X is COZ where Z is OR^4 where R^4 is a methyl or ethyl group or Z is NR^5R^6 where and R^5 is hydrogen and R^6 phenyl, P^1 is hydrogen, benzyl or silyl group and W represents =O or OP^2 where P^2 is a methyl group.

The invention is illustrated by the following Examples.

Example 1 - Preparation of Chlorolactol methyl acetal ((2S,4R)-2-(chloromethyl)-6-methoxytetrahydro-2H-pyran-4-ol), a compound of Formula 1 where Y = Cl, P^1 = H and W = $-OP^2$, in which P^2 = Me.

Crude chlorolactol (15g) was dissolved in methanol (150ml) and heated to 40°C for 2 hours in the presence of 0.1ml sulphuric acid. The solvent was removed by rotary evaporation to afford the product as a dark brown flowing oil. The product was dissolved in DCM and washed with sodium bicarbonate solution. The solvent was removed by rotary evaporation to afford the product as a dark brown flowing oil, which was purified by column chromatography (16.1g) m/z 179, 149 and 113; ^{1}H nmr $CDCl_3$ 3.6-3.7 (m 2H), 4.1 (m 1H), 1.5-1.6 (m 2H), 4.0 (m 1H), 1.3-1.6 (m 2H), 4.9 (m 1H), 3.3 & 3.5 (s 3H); ^{13}C nmr $CDCl_3$ 32, 36, 45, 55&56, 64, 65, 94.

Example 2 - Preparation of O-benzyl-chlorolactol methyl acetal ((2S,4R)-4-(benzyloxy)-2-(chloromethyl)-6-methoxytetrahydro-2H-pyran), a compound of Formula 1 where Y = Cl, P^1 = Bz and W = –OP^2, in which P^2 = Me.

Chlorolactol methyl acetal (1g) was dissolved in THF (5ml) and charged to sodium hydride (0.33g 60% in mineral oil) in THF (5ml) at room temperature. Benzyl bromide (1.9g) was added dropwise and the mass heated to 80°C for 2 hours. Methanol (2ml) was added and the mass was partitioned between DCM/ water, and was then washed with water. The organic phase was dried and the solvent was removed by rotary evaporation to afford an orange flowing oil (2.1g). m/z 270; 238; 203; 132; 91; ^{1}H nmr $CDCl_3$ 1.6-2.0 (m 4H), 3.4 & 3.5 (s 3H), 3.6 (m 2H), 3.8 (m 1H), 4.0 (m 1H), 4.5 (m 2H), 4.7 (m 1H), 7.3-7.5 (m 5H); ^{13}C nmr $CDCl_3$ 32&33, 46, 55&56, 58, 66, 74, 96&98, 128-131.

Example 3 - Preparation of Cyano-O-benzyl lactol methyl acetal ([(2R,4R)-4-(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl]acetonitrile), a compound of Formula 2 where P^1 = Bz and W = –OP^2, in which P^2 = Me.

O-benzyl-chlorolactol methyl acetal (5g) was dissolved in DMSO (50ml) containing Potassium cyanide (5g) and heated for 4 days at 80°C. The mass was then partitioned between diethylether (50ml) and water (50ml). The organic phase was removed, dried and the solvent was removed by rotary evaporation to afford a dark oil, which was purified by column chromatography m/z 261, 229, 184, 123, 107, 91; ^{1}H nmr $CDCl_3$ 1.6-1.9 (m 4H), 2.5 (m 2H), 3.4 & 3.5 (s 3H), 3.6 (m 1H), 3.8 (m 1H), 4.5 (s 2H); ^{13}C nmr $CDCl_3$ 24, 34, 36, 54, 56, 58, 68, 73, 98&100, 117, 122-128.

Example 4 - Preparation of Aminoethyl-O-benzyl-lactol methyl acetal (2-[(2R,4R)-4-(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl]ethanamine), a compound of Formula 3 where P^1 = Bz and W = –OP^2, in which P^2 = Me.

Borane –THF complex (1 molar solution) (1.19mls) was charged to a nitrogen purged flask at 10°C and diluted with THF (2.5mls). Cyano-O-benzyl lactol methyl acetal (0.05g) was dissolved into THF (7.5.5mls) at 10°C and charged to the borane. The resultant mixture was then heated at reflux for 9 hours. The mixture was cooled,

quenched with methanol (10ml) and concentrated in vacuo. A further two portions of Methanol (2 x 10mls) were added, and the mixture twice concentrated to dryness. The final concentration afforded an oil (45mg).

TLC (CH_2Cl_2): new spot at Rf=0.05, positive ninhydrin stain, no residual nitrile.

m/z 265, 233, 107, 91; ^{1}H nmr $CDCl_3$ 1.6-1.9 (m, 6H), 3.4 & 3.45 (s, 3H), 3.5 (2H), 3.6 (m, 1H), 3.8 (m, 1H), 4.5 (s, 2H), 4.7 (m, 1H), 7.1 (m, 5H).

^{13}C nmr $CDCl_3$ 24, 26, 34, 36, 54, 56, 58, 68, 73, 98 &100, 122-128.

Example 5 - Preparation of Pyrrole Ester O-benzyl lactol methyl acetal, a compound of Formula 5 where R^1= iPr, R^2= Ph, R^3= 4-FC_6H_4, X= CO_2Et, P^1 = Bz and W = –OP^2, in which P^2 = Me.

Aminoethyl-O-benzyl-lactol methyl acetal (1.00g) was dissolved in THF (10ml). DiketoEster (1.12g) was added, followed by acetic acid (2ml) and the mixture heated to 80°C for 2 days. After concentration in vacuo the reaction mass was partitioned between diethyl ether (10ml) and water (10ml). The organic phase was collected, dried ($MgSO_4$), and the solvent removed in vacuo to afford a brown oil which was purified by column chromatography (0.38g). M/z : 599, 567, 460, 107, 91; ^{1}H nmr $CDCl_3$ 1.15 (t, 3H), 1.3 (d, 6H), 1.6-1.9 (m, 6H), 3.4 & 3.45 (s, 3H), 3.5 (2H), 3.6 (m, 2H), 3.8 (m, 1H), 4.1 (q, 2H), 4.5 (s, 2H), 4.7 (m, 1H), 7.1 (m, 14H).

19F nmr : Shift from 106ppm (DiKeto Ester) to 115ppm (product).

Example 6 - Preparation of Pyrrole Anilide O-benzyl lactol methyl acetal, a compound of Formula 5 where R^1= iPr , R^2= Ph, R^3= 4-FC_6H_4, X=C(O)NHPh, P^1 = Bz and W = –OP^2, in which P^2 = Me.

Pyrrole Ester O-benzyl lactol methyl acetal (0.30g) was dissolved in DMF (5ml). Aniline (1.0g) was added and the mixture heated to 80°C for 18 hours. After cooling, and concentration in vacuo the reaction mass was partitioned between diethyl ether (5ml) and water (5ml). The organic phase was collected, washed further with water (5ml), dried ($MgSO_4$), and the solvent removed in vacuo to afford a brown oil which was purified by column chromatography (0.26g). M/z 646, 614, 507, 107, 91; ^{1}H nmr $CDCl_3$ 1.3 (d, 6H), 1.6-1.9 (m, 6H), 3.4 & 3.45 (s, 3H), 3.5 (2H), 3.6 (m, 2H), 3.8 (m, 1H), 4.5 (s, 2H), 4.7 (m, 1H), 6.8 (br.s 1H), 7.1 (m, 19H).

Example 7 - Preparation of Pyrrole Anilide OH lactol methyl acetal (Lipitor Lactol-OMe) a compound of Formula 5 where R^1= iPr, R^2= Ph, R^3= 4-FC_6H_4, X=C(O)NHPh, P^1 = H and W = –OP^2, in which P^2 = Me.

Pyrrole Anilide O-benzyl lactol methyl acetal (0.15g) was dissolved in Methanol (5ml). 10% Pd/C (0.1g) was added under Nitrogen. The system was flushed with Hydrogen, the heated under an atmosphere of hydrogen for 6 hours. After removal of the

Pd/C by filtration, and concentration of the reaction mass in vacuo, the residual brown oil was purified by column chromatography. M/z 556, 524, 506; ^{1}H nmr $CDCl_3$ 1.3 (d, 6H), 1.6-1.9 (m, 6H), 3.4 & 3.45 (s, 3H), 3.5 (2H), 3.6 (m, 2H), 3.8 (m, 1H), 4.7 (m, 1H), 6.8 (br.s 1H), 7.1 (m, 14H).

Example 8 - Preparation of Pyrrole Anilide OH lactol (Lipitor Lactol), a compound of Formula 5 where R^1= iPr, R^2= Ph, R^3= 4-FC_6H_4, X=C(O)NHPh, P^1 = H and W = –OP^2, in which P^2 = H.

Pyrrole Anilide OH lactol methyl acetal (0.050g) was dissolved in Methanol (2ml), and water (2ml) was added, followed by 0.1N HCl (1ml). After stirring at room temperature for 2 hours, the mixture was concentrated in vacuo to afford the product as a colourless oil. M/z 542, 524, 506; ^{1}H nmr $CDCl_3$ 1.3 (d, 6H), 1.6-1.9 (m, 6H), 3.45 (2H), 3.6 (m, 2H), 3.8 (m, 1H), 5.0(m, 1H), 6.8 (br.s 1H), 7.1 (m, 14H); ^{13}C nmr $CDCl_3$ 91.6ppm (Lactol C); FTIR : 1652cm^{-1} (Amide)

Example 9 - Preparation of Lactone, a compound of Formula 6 where R^1= iPr, R^2= Ph, R^3= 4-FC_6H_4, X= C(O)NHPh, P^1=H

The Pyrrole Anilide OH lactol (35mg, 0.065mmol) in dichloromethane (0.5ml) was added to Dess-Martin periodinane (30mg, 0,07mmol) and stirred at room temperature for 2.5 hours. The reaction was partitioned between 1M sodium hydroxide and diethyl ether. The phases were then separated and the organic volume reduced in vaccuo to afford the crude product oil.

^{1}H nmr 500MHz CDCl3: 9.8, 7.5, 7.28, 7.2, 7.08, 7.02, 6.98, 5.2, 4.5, 4.1, 4.0, 3.9, 3.2, 2.6, 2.4, 1.6, 1.4.

^{13}C nmr 125.72MHz DMSO: 169.6, 165.9, 139.3, 135.9, 134.7, 133.3, 129.4, 128.8, 128.4, 127.5, 127.2, 125.3, 122.9, 120.7, 119.3, 117.6, 115.4, 25.5, 22.1, 22.3, 39.5, 34.5, 72.8, 36.8, 61.0, 38.3.

Example 10 - Preparation of Atorvastatin (hydrolysis of Lactone), a compound of Formula 7 where R^1= iPr, R^2= Ph, R^3= 4-FC_6H_4, X=C(O)NHPh

The lactone (1.1g) was dissolved in ethanol (10ml). Water (2ml) and $Ca(OH)_2$ (0.15g) were added and the suspension warmed to 60°C for 3 hours. A further 10ml of warm water was added, then the mixture allowed to cool slowly to room temperature. The precipitate formed was filtered and dried to give atorvastatin calcium salt (0.3g). The material was identical to an authentic sample by mixed melting point, NMR and mass spectrometry.

Independent Preparation of Pyrrole Anilide OH lactol (Lipitor Lactol), a compound of Formula 5 where R^1= iPr, R^2= Ph, R^3= 4-FC_6H_4, X=C(O)NHPh, P^1 = H and W = $-OP^2$, in which P^2 = H, from an authentic source of Lactone.

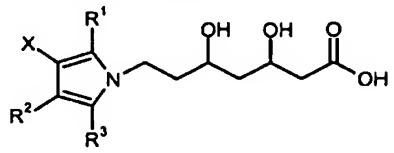
An authentic sample of Lactone (530mg) was dissolved in anhydrous DMF (5ml), followed by imidazole (174mg), then TBDMS chloride (371mg). The mixture was stirred at room temperature. After 6 hours, the reaction was worked up by addition of Et_2O (30ml) and water (30ml). The separated organic phase was further washed with water (2 x 20ml), dried, and concentrated in vacuo to afford silylated lactone as a white powder (470mg, 73%).

The silylated lactone (233mg) was dissolved in anhydrous dichloromethane (5ml), then cooled to –78°C under Nitrogen. DIBAL (0.31ml, 1M in toluene) was added dropwise and the mixture stirred for 10 minutes at -78°C. The mixture was then quenched by addition of 1ml of 10% aqueous Rochelle's salt and allowed to warm to room temperature. After addition of further dichloromethane (10ml) and water (10ml), the phases were separated and the organic phase dried and concentrated in vacuo. The residual oil was purified by column chromatography (50% Et_2O in hexane). FTIR : 1668 cm^{-1} (amide). Stretch at 1735cm^{-1} (Lactone) no longer present.

The silylated lactol (100mg) was dissolved in anhydrous THF. HF.pyridine was added (0.1ml) at 0°C and allowed to warm to room temperature. The mass was quenched with ether/and sodium bicarbonate solution. The phases separated and the aqueous phase back extracted with ether. The organic phases were combined, dried and evaporated to produce and oil (75mg). M/z 542, 524, 506; ^1H nmr $CDCl_3$ 1.3 (d, 6H), 1.6-1.9 (m, 6H), 3.45 (2H), 3.6 (m, 2H), 3.8 (m, 1H), 5.0(m, 1H), 6.8 (br.s 1H), 7.1 (m, 14H); ^{13}C nmr $CDCl_3$ 91.6ppm (Lactol C); FTIR : 1652cm^{-1} (Amide)

CLAIMS

1. A process for the preparation of a compound of formula (7) or salts thereof:

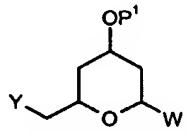


wherein

R^1 represents a hydrogen or a hydrocarbyl group
R^2 represents a hydrogen or substituent group
R^3 represents a hydrogen or a hydrocarbyl group
X represents a hydrogen or substituent group

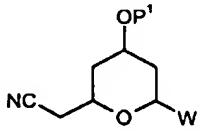
which comprises

a) cyanating a compound of formula (1):

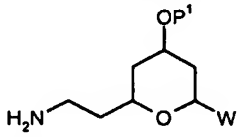


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group,

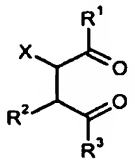
to give a compound of formula (2):



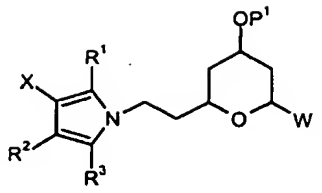
b) reducing the compound of formula (2) to give a compound of formula (3):



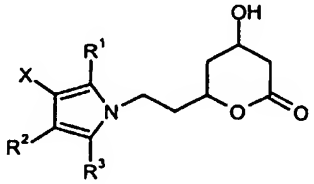
c) coupling the compound of formula (3) with a compound of formula (4):



to give a compound of formula (5):

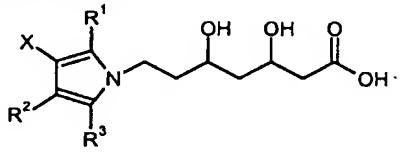


d) when W represents -OP^2, deprotecting and then oxidising the compound of formula (5) to give a compound of formula (6):

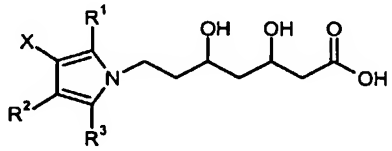


and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, and removal of any remaining protecting groups, to give a compound of formula (7) or salts thereof:



2. A process according to Claim 1 for the preparation of a compound of formula (7) or salts thereof:



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group

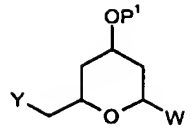
R^2 represents an aryl group, preferably a phenyl group

R^3 represents an aryl group, preferably a 4-fluorophenyl group

X a group of formula –COZ, wherein Z represents -OR^4, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or –NR^5R^6, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl

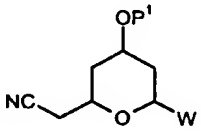
which comprises

a) cyanating a compound of formula (1):

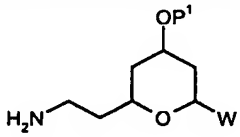


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group,

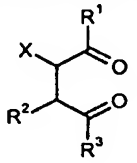
to give a compound of formula (2):



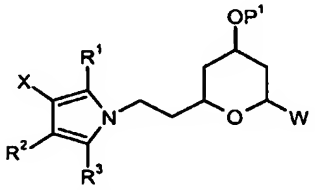
b) reducing the compound of formula (2) to give a compound of formula (3):



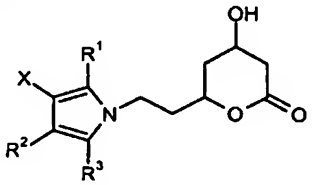
c) coupling the compound of formula (3) with a compound of formula (4):



to give a compound of formula (5):

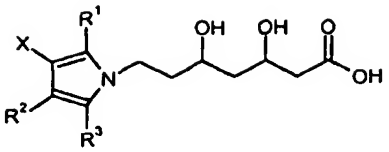


d) when W represents $-OP^2$, deprotecting and then oxidising the compound of formula (5) to give a compound of formula (6):



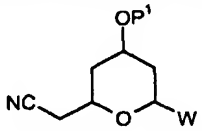
and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, and removal of any remaining protecting groups, to give a compound of formula (7) or salts thereof:

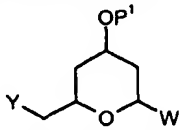


3. A process according to Claim 2 wherein R^1 is an isopropyl group, R^2 is a phenyl group, R^3 is a 4-fluorophenyl group and X is a $-CO_2Me$, $-CO_2Et$ or -CONHPh group

4. A process for the preparation of a compound of formula (2):

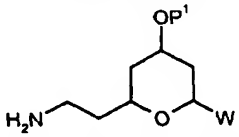


which comprises cyanating a compound of formula (1):

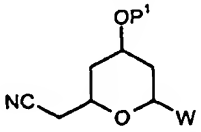


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

5. A process for the preparation of a compound of formula (3):



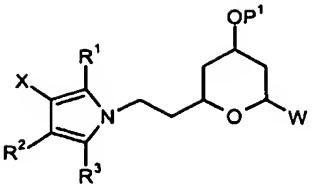
which comprises reduction of a compound of formula (2):



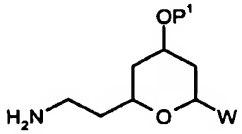
wherein P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

6. A process according to Claim 4 or Claim 5 wherein P^1 represents a benzyl or a silyl group, and W represents =O or $-OP^2$, in which P^2 represents a methyl group

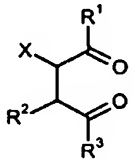
7. A process for the preparation of a compound of formula (5):



which comprises coupling the compound of formula (3):



with a compound of formula (4):



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

R^2 represents an aryl group, preferably a phenyl group;

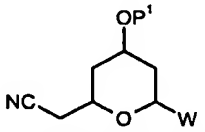
R^3 represents an aryl group, preferably a 4-fluorophenyl group;

X a group of formula –COZ, wherein Z represents $-OR^4$, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or $–NR^5R^6$, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl;

P^1 represents hydrogen or a protecting group, preferably a benzyl or silyl group; and

W represents =O or $–OP^2$, in which P^2 represents hydrogen or a protecting group, preferably OP^2 where P^2 is a methyl group.

8. A compound of formula (2):

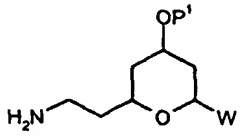


wherein P^1 represents hydrogen or a protecting group, and W represents =O or $–OP^2$, in which P^2 represents hydrogen or a protecting group.

9. A compound according to Claim 8 wherein P^1 is a protecting group and preferably W represents $–OP^2$, and more preferably P^1 and P^2 are different.

10. A compound according to Claim 9 wherein P^1 is a benzyl or silyl group and W represents OP^2 where P^2 is a methyl group.

11. A compound of formula (3):

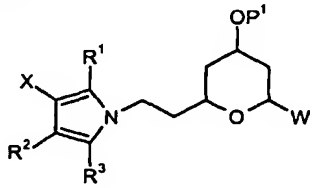


wherein P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

12. A compound according to Claim 11 wherein P^1 is a protecting group and preferably W represents $-OP^2$, and more preferably P^1 and P^2 are different.

13. A compound according to Claim 12 wherein P^1 is a benzyl or silyl group and W represents OP^2 where P^2 is a methyl group.

14. A compound of formula (5):



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

R^2 represents an aryl group, preferably a phenyl group;

R^3 represents an aryl group, preferably a 4-fluorophenyl group;

X a group of formula –COZ, wherein Z represents $-OR^4$, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or $-NR^5R^6$, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl;

P^1 represents hydrogen or a protecting group; and

W represents $-OP^2$, in which P^2 represents hydrogen or a protecting group.

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003206

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 C07D309/10 C07D309/30 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92/06968 A (WARNER LAMBERT CO) 30 April 1992 (1992-04-30) the whole document; in particular, the examples 1 (Method F), 2 and 4	1-14
P,X	WO 2004/027075 A (GREENBERG WILLIAM ; WONG KELVIN (US); DIVERSA CORP (US); SWANSON RONAL) 1 April 2004 (2004-04-01) page 34, line 1 - page 35, line 4 figures 8,10,11	1-5,7,8, 11
E	WO 2004/096788 A (MINK DANIEL ; WOLBERG MICHAEL (DE); SEREINIG NATASCHA (NL); BOESTEN WI) 11 November 2004 (2004-11-11) claims 1,6,17 examples 1,3	4,5,8,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 2004	30/12/2004

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (January 2004)

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